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Communication

An Azafluorenone Alkaloid and a Megastigmane from *Unonopsis lindmanii* (Annonaceae)

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O alcalóide azafluorenona 5,8-dimetóxi-7-hidróxi-1-metil-4-azafluoren-9-ona e o megastigmano (–)-(5*R**, 6*S**)-megastigman-3-ona-10,7-olidio foram isolados das partes aéreas de *Unonopsis lindmanii* (Annonaceae), juntamente com os compostos conhecidos (3*S**, 5*S**, 8*R**)-3,5-di-hidróxi-megastigma-6,7-dien-9-ona (*grasshopper ketone*), *N-trans*-feruloiltiramina, (–)-anonaína, (–)-asimilobina, liriodenina e (–)-siringaresinol. Este é o primeiro relato da presença de megastigmanos em Annonaceae. As estruturas dos compostos foram elucidadas com base em dados espectroscópicos.

The azafluorenone alkaloid 5,8-dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one and the megastigman (–)-(5*R**, 6*S**)-megastigman-3-one-10,7-olide were isolated from aerial parts of *Unonopsis lindmanii* (Annonaceae), along with the known compounds (3*S**, 5*S**, 8*R**)-3,5-dihydroxy-megastigma-6,7-dien-9-one (grasshopper ketone), *N-trans*-feruloyltyramine, (–)-anonaine, (–)-asimilobine, liriodenine and (–)-syringaresinol. This is the first description of the presence of megastigmanes in Annonaceae. The structures of the compounds were elucidated based on spectroscopic data.

Keywords: *Unonopsis lindmanii*, Annonaceae, alkaloids, azafluorenone, megastigmanes

Introduction

Annonaceae is one of the largest families of the Magnoliide subclass, with approximately 135 genera and 2300 species, mostly pantropical. In Brazil, Annonaceae comprises about 26 genera and 260 species and has a great significance in the Brazilian vegetation.[1,2] Although the occurrence of different types of alkaloids has been frequently described, compounds with unusual skeletons, such as acetogenins,[3,4] polyacetylenes,[5] cyclopeptides,[6,7] styryl lactones,[8-10] indolidinoids[11] and monoterpene glucosides[12] have been recently reported, most of them showing biological activities as anticancer,[3,13,14] antimicrobial,[11,15] cytotoxic,[10,16] antiinflamatory[7,17] and antiprotozoal.[18]

As part of our research on the chemistry of Annonaceae species,[16,19-22] the isolation and structural elucidation of two new compounds from the aerial parts of *Unonopsis lindmanii* R. E. Fries (R. E. Fries) are discussed: the azafluorenone alkaloid 5,8-dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one (**1**) and the megastigman (–)-(5*R**, 6*S**)-megastigman-3-one-10,7-olide (**2**) (Figure 1). *U. lindmanii* is a medium-sized tree, which is widely distributed in the Central-Western region of Brazil occurring mainly in riparian forest and

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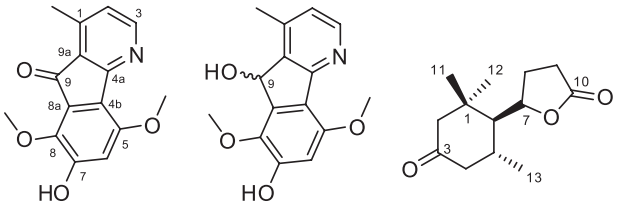
cerrado.[1,23] The chemical composition of *Unonopsis* genus was not widely investigated, and previous studies revealed the presence of some aporphines, bisaporphines, phenantrenes and azafluorenone alkaloids[18,22,24,25] and polycarpol.[26] The present phytochemical study of *U. lindmanii* also led to the isolation and identification of the known compounds grasshopper ketone,[27] liriodenine,[28] (–)-anonaine,[29] (–)-asimilobine,[29] (–)-siringaresynol[30] and *N-trans*-feruloyltyramine.[31] The structural elucidation of the compounds was established on the basis of spectroscopic techniques.



1 **1a** **2**

Figure 1. Chemical structures of compounds **1**, **1a** and **2**.

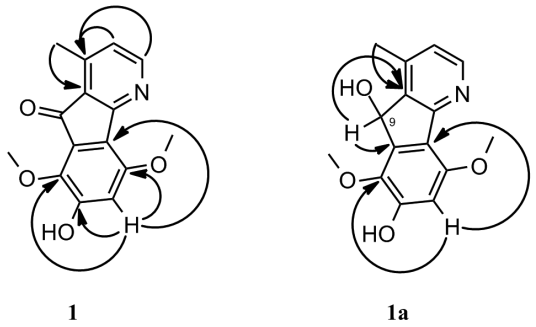
Results and Discussion

The ethanolic extract of the heartwood of *U. lindmanii* was chromatographed on a silica gel column and then on a Sephadex LH-20 column to afford compound **1**. The positive HRESIMS of **1** revealed a pseudo-molecular ion at *m/z* 272.0957 $[M + H]^+$, consistent with the molecular formula $C_{15}H_{13}NO_4$. The presence of a carbonyl group was demonstrated by an IR band at 1649 cm^{-1}. The ^1H nuclear magnetic resonance (NMR) spectrum of **1** (Table 1) showed three signals of aromatic hydrogens at δ_H 6.91 (s, H-6), 6.86 (d, *J* 5.2 Hz, H-2) and 8.23 (d, *J* 5.2 Hz, H-3), two methoxyl groups at δ_H 3.92 (s, 5-OCH_3) and 4.01 (s, 8-OCH_3), and a signal of a methyl bonded to an aromatic ring at δ_H 2.59 (s, 1-CH_3). The ^{13}C NMR spectrum of **1** (Table 1) contained fifteen signals attributed to a conjugated carbonyl (δ_C 190.7), three aromatic protonated sp^2 carbons bound to hydrogens, eight sp^2 aromatic carbons without hydrogens attached, two methoxyl groups and one methyl. Atomic connectivity was established using COSY, one-bond (HSQC), long-range (HMBC) ^1H-^{13}C NMR correlation experiments and nuclear Overhauser effect spectroscopy (NOESY) (Figure 2). The ^{13}C NMR spectrum of **1** showed a signal for only one methoxyl group attached to *ortho*-disubstituted carbon at δ_C 61.1, which was correlated in HSQC with the ^1H NMR signal at δ_H 4.01 and in HMBC with the signal at δ_C 142.5. These correlations imply that the aromatic hydrogen at δ_H 6.91 must not be vicinal to this methoxyl group. The second methoxyl signal at δ_H 3.92 showed one-bond correlation with the ^{13}C NMR signal at δ_C 56.5 and long-range correlation with the signal at δ_C 156.4. In the HMBC experiment, the aromatic hydrogen at δ_H 6.91 showed strong correlations with the carbons at δ_C 119.2, 142.5, 147.2 and 156.4, suggesting two possible structures for this compound: 5,8-dimethoxy-7-hydroxy or 5,8-dimethoxy-6-hydroxy. A comparison between the ^1H NMR chemical shifts with the 5,8-dimethoxy-6-hydroxy-1-methyl-azafluorenone (kinabaline)[32] indicated that H-7 displays a higher field resonance (δ_H 6.34) when compared to that (δ_H 6.91) in compound **1**. This evidence allowed the assignment of the resonance at δ_C 61.1 to 8-OMe, δ_C 142.5 to C-8, δ_C 56.5 to 5-OMe, δ_C 156.4 to C-5, δ_C 147.2 to C-7 and δ_C 119.2 to C-4b. Therefore, the most likely structure for the new alkaloid must be 5,8-dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one. This structure received further support from reduction of **1**, which yielded **1a**.

The compound **1a** was obtained via reduction of **1** with $NaBH_4$. In the ^1H NMR spectrum of **1a** (Table 1), the presence of a signal at δ_H 5.70 (s, H-9) was consistent

Table 1. NMR spectroscopic data for compounds **1** ($CDCl_3$) and **1a** (C_2D_6CO) (300 MHz ^1H and 75 MHz ^{13}C)

Position	**1**		**1a**	
	δ_C, type	δ_H (m, *J* / Hz)	δ_C, type	δ_H (m, *J* / Hz)
1	149.2, C		147.7, C	
2	124.6, CH	6.86 (d, 5.2)	123.9, CH	7.15 (d, 5.0)
3	148.6, CH	8.23 (d, 5.2)	146.6, CH	8.30 (d, 5.0)
4a	164.0, C		149.5, C	
4b	119.2, C		116.6, C	
5	156.4, C		158.3, C	
6	101.5, CH	6.91 (s)	103.0, CH	6.97 (s)
7	147.2, C		144.4, C	
8	142.5, C		137.7, C	
8a	129.6, C		144.1, C	
9	190.7, C		73.6, CH	5.70 (s)
9a	126.0, C		139.0, C	
1-CH_3	17.3, CH_3	2.59 (s)	17.8, CH_3	2.57 (s)
5-OCH_3	56.5, CH_3	3.92 (s)	56.9, CH_3	3.91 (s)
8-OCH_3	61.1, CH_3	4.01 (s)	61.0, CH_3	3.82 (s)



1 **1a**

Figure 2. HMBC (H ⌒ C) correlations of **1** and **1a**.

with the expected product. The HMBC spectrum of **1a** showed hydrogens of the methyl attached to C-1 correlating strongly with carbons at δ_C 147.7, 123.9 and 139.0 assigned to C-1, C-2 and C-9a, respectively. In this same experiment, the hydrogen H-9 correlates strongly with two carbons, one C-9a (δ_C 139.0, as defined previously) and the other at δ_C 144.1, corresponding to the carbon in equivalent position to C-9a, i.e., C-8a. Moreover, it was observed that the hydrogen δ_H 6.97 (H-6) correlates strongly with the carbons at δ_C 116.6 (C-4b) and 137.7 (C-8), which were located in *meta* position in relation to H-6, but that did not correlate with the carbon at δ_C 144.1 (C-8a). This observation allowed us to determine the correct position of hydrogen H-6 (δ_H 6.97). Consequently, the structure of **1a** corresponds to that displayed in Figure 1.

Compound **2** was isolated as a brownish-yellow amorphous solid from the $CHCl_3$ leaf extract, after chromatographic steps using silica gel column. From HRESIMS spectrum of **2**, a pseudo-molecular ion peak at *m/z* 225.1551 $[M + H]^+$ was obtained, corresponding to the molecular formula $C_{13}H_{20}O_3$. In the ^1H NMR spectrum of **2** (Table 2), two methyl singlets were observed at δ_H 0.76 and 1.03 (H-11 and H-12, respectively), and a doublet at δ_H 1.04 (d, *J* 6.4 Hz) was attributed to the methyl H-13 hydrogen. The signal at δ_H 2.05 (dd, *J* 13.4 and 2.0 Hz) was assigned to H-$2_{equatorial}$ hydrogen, with geminal coupling constant of 13.4 Hz and a $^4J_{Wequatorial\text{-}equatorial}$ coupling of 2.0 Hz with the H-$4_{equatorial}$, appearing as a double doublet, while the H-2_{axial} appeared as a doublet at δ_H 2.25 (d, *J* 13.4 Hz) with geminal coupling constant of 13.4 Hz. The signals at δ_H 2.00 (d, *J* 11.2 Hz) and 2.29 (dd, *J* 11.2 and 2.0 Hz) were assigned to the methylenic hydrogens H-$4_{axial/equatorial}$, respectively, supported by HSQC spectrum. The analysis of the ^{13}C NMR spectrum revealed the presence of 13 carbons, suggesting a megastigmane skeleton. The signals at δ_C 211.0 and 176.3 were attributed to the carbonyl at C-3 and the carboxyl at C-10, the last signal indicating a possible lactone ring. A signal at δ_C 71.9 was assigned to C-7, that one at δ_C 52.1 to C-6, and the signals at δ_C 20.6, 29.9 and 20.9 assigned to the three methyl carbons C-11, C-12 and C-13, respectively. Correlations between C-3 and H-2 and H-4 were visualized in the HMBC spectrum, as well as $^3J_{C\text{-}H}$ correlations between C-10 and H-7. The C-13 signal at δ_C 20.9, which had its position confirmed through HMBC and HSQC experiments, was consistent with the equatorial position of this group, in comparison with spectral data from previously described analogues.[33] In the NOESY experiment, some important correlations were observed between H-11 (δ_H 0.76), which is in axial position, and H-5 (δ_H 1.79), confirming the configuration at position 5; between H-11 and H-8 (δ_H 1.62) and between H-5 and H-7 (δ_H 4.14), indicating the position of the lactone ring (Figure 3). These assignments were checked by COSY, HSQC and HMBC analyses, and the relative configuration was based on correlations in the NOESY experiment, confirming the structure of **2** as (–)-(5*R**, 6*S**)-megastigman-3-one-10,7-olide.

Table 2. NMR spectroscopic data for compound **2** (300 MHz ^1H and 75 MHz ^{13}C, $CDCl_3$)

Position	δ_C, type	δ_H (m, *J* / Hz)	HMBC (C → H)
1	39.2, C		H-2/H-11/H-12
2	56.2, CH_2	2.25 (d, 13.4); 2.05 (dd, 13.4; 2.0)	H-6/H-11/H-12/H-4
3	211.0, C		H-2/H-4
4	50.1, CH_2	2.00 (d, 11.2); 2.29 (dd, 11.2; 2.0)	H-6
5	36.3, CH	1.79 (m)	H-13
6	52.1, CH	1.05 (d, 6.2)	H-2/H-4/H-11/ H12/H-13
7	71.9, CH	4.14 (m)	
8	24.1, CH_2	1.62 (m)	H-7
9	36.5, CH_2	1.85 (m)	
10	176.3, C		H-7
11	20.6, CH_3	0.76 (s)	H-12
12	29.9, CH_3	1.03 (s)	H-2/H-11
13	20.9, CH_3	1.04 (d, 6.4)	H-4

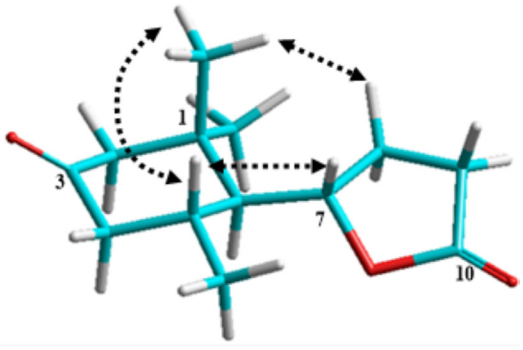


Figure 3. Selected NOESY correlations of **2**.

Conclusions

Although alkaloids are a common theme in Annonaceae, the occurrence of azafluorenones is rare and restricted to this family. Some hypotheses for the biosynthesis of these alkaloids are raised based on different sources, some suggesting their origin from oxaporphinic alkaloids, supported by the co-occurrence of these compounds.[34] Other authors indicated a possible route from a polyketide pathway[34] or from a shikimic acid intermediate bound to a glutamic acid unit as a base to the skeleton of these molecules.[35] Despite several proposals, the biosynthetic pathway to the formation of azafluorenones remains unknown. This study

contributed to the expansion of the chemical characterization of the *Unonopsi*s genus since the compounds grasshopper ketone, (–)-syringaresinol and *N-trans*-feruloyltyramine are being described for the first time in *Unonopsis*. To the best of our knowledge, this is the first time that the presence of megastigmanes in Annonaceae is described, indicating the importance of continuing the investigation of this family as a source of novel molecules.

Experimental

General procedures

Silica gel (70-230 mesh, Merck) and Sephadex LH-20 (Amersham Biosciences) were used for column chromatography (CC), whereas silica gel 60 GF_{254} was employed for analytical (0.50 mm) and preparative (1.0 mm) thin layer chromatography (TLC). The ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, on a Bruker DPX-300 spectrometer using $CDCl_3$ (Aldrich) and acetone-d_6 (Aldrich) as solvents and tetramethylsilane (TMS) as an internal standard. The IR spectra were obtained on a Perkin-Elmer 783 spectrometer and the specific optical rotations on a Perkin-Elmer 341 MS polarimeter. Mass spectra were obtained in Agilent Ultra Q-TOF mass spectrometer with electrospray ionization.

Plant material

Heartwood and leaves of *Unonopsis lindmanii* were collected in March 2005 in Pantanal (Mato Grosso do Sul, Brazil) and identified by Dr. Renato Mello Silva (University of São Paulo, Brazil). A voucher specimen (No. 4730) was deposited in the Herbarium GC/MS (Universidade Federal do Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil).

Extraction and isolation

Dried heartwood (2.9 kg) was subjected to maceration in ethanol for 7 days, yielding 28.5 g of ethanolic extract. The extract was dried under reduced pressure and then resuspended in MeOH, resulting in a precipitate and a supernatant. The composition of the supernatant part was essentially sugars, and the precipitate (6.0 g) was submitted to column chromatography on silica gel with a gradient of polarity hexane-ethyl acetate-methanol, yielding fractions A-D. Fraction A was a mixture of β-sitosterol and stigmasterol (40.3 mg). Fraction B (38 mg) was re-chromatographed on a Sephadex LH-20 column, using ethyl acetate as solvent, yielding the alkaloid 5,8-dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one (**1**) (6.3 mg). Fraction C (248.2 mg) was submitted to CC on Sephadex LH-20 using CH_2Cl_2:MeOH (1:1) as eluent, yielding the lignan (–)-syringaresinol (38.8 mg) and *N-trans*-feruloyltyramine (35.4 mg). Fraction D (23.5 mg), containing the alkaloids (–)-anonaine (6.0 mg) and (–)-asimilobine (3.6 mg), was fractionated by CC Sephadex LH-20 using CH_2Cl_2:MeOH (1:1) as eluent. Dried leaves (950 g) of *U. lindmanii* were extracted in $CHCl_3$ in basic medium (10% NH_4OH, pH 9) under constant stirring for 5 days, yielding 21.5 g of crude extract. This extract was partitioned using 5% HCl and $CHCl_3$. The pH value of the acidic aqueous fraction was adjusted to 9 with NH_4OH and then extracted with $CHCl_3$. The chloroform phases were concentrated under reduced pressure, yielding 1.6 g from the chloroform extract. This extract was submitted to CC on silica, yielding megastigmanes (–)-(5*R**, 6*S**)-megastigman-3-one-10,7-olide (**2**) (7.8 mg) and grasshopper ketone (**3**) (10.6 mg), and the alkaloids liriodenine (5.7 mg) and (–)-asimilobine (13.3 mg).

5,8-Dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one (**1**): yellow amorphous solid; IR (KBr) ν_{max}/cm^{-1} 3422, 2917, 2850, 1680, 1464, 1246, 1117, 1036. For ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* (rel. int.) 272.0957 $[M + H]^+$ (11) ($C_{15}H_{13}NO_4$ $[M + H]^+$ calc. 272.27596), 239.06 (43), 211.06 (100), 183.07 (18), 155.12 (7); LRESIMS (rel. int.) *m/z* 272.09 $[M + H]^+$ (11), 239 (43), 211 (100), 183 (18), 155 (7).

5,8-Dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-ol (**1a**): $NaBH_4$ (1.4 mg) was added to a solution of **1** (5.3 mg) in isopropanol (1.5 mL), and the mixture was stirred at room temperature for 1 h. After completion, the reaction was quenched with H_2O and extracted with 3 × 5 mL of CH_2Cl_2. Layers were separated and washed with H_2O. Anhydrous Na_2SO_4 was added to the organic fraction, filtered, concentrated to dryness, and purified by preparative TLC on silica gel developed in CH_2Cl_2, to produce 3.2 mg (yield 57.1%) of the reduced product as a pale yellow amorphous solid, which was identified as **1a** by NMR analysis (Table 1).

(5*R**, 6*S**)-Megastigman-3-one-10,7-olide (**2**): brownish-yellow amorphous solid; $[\alpha]_D^{20}$ –54.34 (*c* 0.0024, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1} 3391, 2931, 2851, 1655, 1456, 1122, 1047; ^{1}H and ^{13}C NMR data (see Table 2); HRESIMS *m/z* (rel. int.) 225.1551 $[M + H]^+$ (100) ($C_{13}H_{20}O_3$ $[M + H]^+$ calc. 225.30404), 248.13 (24), 236.13 (34), 222.14 (30); LRESIMS (rel. int.) *m/z* 225 $[M + H]^+$ (100), 248 (24), 236 (34), 222 (30).

Supplementary Information

Supplementary information (^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **1a** and **2**) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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